

F. TENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION
(PCT Rule 61.2)

Date of mailing (day/month/year) 26 February 2001 (26.02.01)	ETATS-UNIS D'AMERIQUE in its capacity as elected Office
International application No. PCT/US00/15016	Applicant's or agent's file reference X-12437
International filing date (day/month/year) 08 June 2000 (08.06.00)	Priority date (day/month/year) 15 July 1999 (15.07.99)
Applicant CHEN, Shu, Hui et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

19 January 2001 (19.01.01)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p>	<p>Authorized officer</p> <p>A. Karkachi</p> <p>Telephone No.: (41-22) 338.83.38</p>
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PENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

MUSSER, Arlene, K.
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 14 December 2001 (14.12.01)			
Applicant's or agent's file reference X-12437	IMPORTANT NOTIFICATION		
International application No. PCT/US00/15016	International filing date (day/month/year) 08 June 2000 (08.06.00)		

1. The following indications appeared on record concerning:

the applicant the inventor the agent the common representative

Name and Address SUN, Xicheng, David 9929 Brightwater Drive Noblesville, IN 46060 United States of America	State of Nationality CN	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

the person the name the address the nationality the residence

Name and Address SUN, Xicheng, David 923 Grays Peak Drive Superior, CO 80027 United States of America	State of Nationality CN	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Marie-José DEVILLARD
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

<p>To:</p> <p>Cohen, Charles E ELI LILLY AND COMPANY Lilly Corporate Center Indianapolis, Indiana 46285 ETATS-UNIS D'AMERIQUE</p>	<p>RECEIVED</p> <p>NOV 19 2001</p> <p>ELI LILLY & COMPANY PATENT DIVISION</p>	<p>PCT</p> <p>NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Rule 71.1)</p>
		<p>Date of mailing (day/month/year)</p>
		<p>09.11.2001</p>
<p>Applicant's or agent's file reference X-12437</p>		<p>IMPORTANT NOTIFICATION</p>
<p>International application No. PCT/US00/15016</p>	<p>International filing date (day/month/year) 08/06/2000</p>	<p>Priority date (day/month/year) 15/07/1999</p>
<p>Applicant ELI LILLY AND COMPANY et al.</p>		
<p>1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.</p> <p>2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.</p> <p>3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.</p> <p>4. REMINDER</p> <p>The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).</p> <p>Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.</p> <p>For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.</p>		

<p>Name and mailing address of the IPEA/</p> <p>European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016</p>	<p>Authorized officer</p> <p>Cardenas, C</p> <p>Tel. +31 70 340-3370</p>
	

PATENT COOPERATION TREATY
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X-12437	FOR FURTHER ACTION	
See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)		
International application No. PCT/US00/15016	International filing date (day/month/year) 08/06/2000	Priority date (day/month/year) 15/07/1999
International Patent Classification (IPC) or national classification and IPC C07K7/06		
<p>Applicant ELI LILLY AND COMPANY et al.</p>		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 7 sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input checked="" type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 		

Date of submission of the demand 19/01/2001	Date of completion of this report 09.11.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Groenendijk, M Telephone No. +31 70 340 3715



INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

International application No. PCT/US00/15016

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-3,5,7-50	as originally filed		
4,6	as received on	12/07/2001 with letter of	12/07/2001

Claims, No.:

1 (part),2 (part), 5 (part),6,7 (part), 12-16	as originally filed		
1 (part),2 (part), 3,4,5 (part),7 (part), 8-11	as received on	12/07/2001 with letter of	12/07/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/15016

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):
(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- the entire international application.
- claims Nos. 16 with respect to industrial applicability.

because:

- the said international application, or the said claims Nos. 16 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- the written form has not been furnished or does not comply with the standard.
- the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability:
citations and explanations supporting such statement**

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/15016

1. Statement

Novelty (N)	Yes: Claims 1-16
	No: Claims
Inventive step (IS)	Yes: Claims 4,5,10,11
	No: Claims 1-3,6-9,12-16
Industrial applicability (IA)	Yes: Claims 1-15
	No: Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/15016

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 16 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1:FEBS Letters, 355(1994), 96-100

D2:Bioorg.Med.Chem.Lett., 10(18), 2000, 2101-2105

I.NOVELTY

In view of the available prior art the claims 1-16 are considered to be novel under Art.33(2) PCT.

II.INVENTIVE STEP

- 1)The closest prior art is considered to be D1 disclosing pseudomycin analogs having antifungal activity.
- 2)The compounds of the present application differ from said prior art compounds essentially in the presence of some specified substituents on at least one of the amino acid residues Lys, Dab1 or Dab2. The resulting compounds exhibit less toxic side-effects.
- 3)The problem to be solved may therefore be considered to be the provision of pseudomycin analogs having less toxic side-effects.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/15016

4) In the prior art there was no indication or suggestion that the present substitution pattern would result in less toxic side-effects without being detrimental to the activity of the compounds. Consequently an inventive step can be acknowledged to those compounds which actually solve the problem posed.

5) However the present claims 1-3,6-9 and 12 and the related claims 13-16 are encompassing compounds with a very broad substitution pattern in the side-chain. Having regard to said plethora of side-chain substituents it is considered to be very unlikely that all of said substituents result in active compounds, which actually can be illustrated by D2, disclosing side-chain residues having aromatic moieties which are encompassed by the present claims and which lack an acceptable activity (e.g., see Table I). Moreover said claims also encompass very short side-chains which also very unlikely can be considered to exhibit an acceptable activity.

Therefore in order to acknowledge an inventive step to said claims their scope should either have been restricted to the compounds demonstrated to be active or it should have been justified by additional experimental data. In the absence of both restriction and justification of scope said claims 1-3,6-9 and 12 are considered to lack an inventive step under Art.33(3) PCT.

For the assessment of the present claim 16 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the international application

In several positions in the description the application contains the expression "incorporated by reference". However the application should, regarding the essential features of the invention, be self-contained, that is, capable of being understood without

INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/US00/15016

reference to any other document. Consequently said expression should have been deleted from the description and, if necessary, said subject-matter by reference should expressly have been incorporated into the description, subject to the restrictions under the Articles 19(2) and 34(2)(b) PCT (see PCT Guidelines CII, 4.17-4.18).

Re Item VIII

Certain observations on the international application

The claims 1-3 and 7-9 contain expressions like "aryl", "heteroaryl", "cycloheteroalkyl" and "alkoxy" without further definition, which renders the scope of said claims unclear under Art.6 PCT. In response the applicant has submitted that said definitions are present in the description and consequently the scope of the claims should be considered to be clear under Art.6 PCT.

However an independent claim should **clearly specify** all of the essential features needed to define the invention (PCT Guidelines C-III,4.1-4.7a). Moreover the expression "aryl" in the description is open-ended and undefined substitution is allowed in both aryl- and alkyl-based moieties. Hence this objection is maintained.

TENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference X-12437	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 00/ 15016	International filing date (day/month/year) 08/06/2000	(Earliest) Priority Date (day/month/year) 15/07/1999
Applicant ELI LILLY AND COMPANY et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :
 - contained in the international application in written form.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority in written form.
 - furnished subsequently to this Authority in computer readable form.
 - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished
- 2. Certain claims were found unsearchable (See Box I).
- 3. Unity of Invention is lacking (see Box II).
- 4. With regard to the title,
 - the text is approved as submitted by the applicant.
 - the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

—
 None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/15016

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K7/06 A61K38/08 A61P31/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category ^o	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	A BALLIO ET AL: "Novel bioactive lipodepsipeptides from <i>Pseudomonas syringae</i> : the pseudomycins" FEBS LETTERS, NL, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 355, no. 1, 21 November 1994 (1994-11-21), pages 96-100, XP002125309 ISSN: 0014-5793 cited in the application the whole document ---	1-16
A	US 5 837 685 A (HARRISON LESLIE A ET AL) 17 November 1998 (1998-11-17) cited in the application the whole document ---	1-16 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search 10 October 2000	Date of mailing of the international search report 17/10/2000
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Authorized officer Groenendijk, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/15016

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 576 298 A (STROBEL GARY A ET AL) 19 November 1996 (1996-11-19) cited in the application the whole document ----	1-16
T	CHEN E.A.: "Syntheses and biological evaluation of novel pseudomycin side-chain analogues. Part 2" BIOORG.MED.CHEM.LETT., vol. 10, no. 18, 2000, pages 2107-2110, XP004208322 the whole document ----	1-16
T	JAMISON E.A.: "Syntheses and antifungal activity of pseudomycin side-chain analogues. Part 1" BIOORG.MED.CHEM.LETT., vol. 10, no. 18, 2000, pages 2101-2105, XP004208321 the whole document -----	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/15016

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5837685 A	17-11-1998	US 5576298 A	US 5981264 A	19-11-1996 09-11-1999
US 5576298 A	19-11-1996	US 5981264 A	US 5837685 A	09-11-1999 17-11-1998